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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/483,434	01/14/2000	JEFFERY L. MILLER	14014.0360	8390

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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/21/2003

23

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application N .	Applicant(s)	
	09/483,434	MILLER ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr.	1636	

-- Th MAILING DATE f this communication appears on the cover she t with the correspondenc address --

Peri d f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,7,9,10,17 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *3,9 and 10* is/are allowed.

6)☒ Claim(s) *7,17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Receipt is acknowledged of a proposed After-Final amendment, filed 2/21/03 as Paper No. 22, in which several changes to the claims were proposed. The proposed amendment has been entered into the file, as it does not appear to generate new issues and is a substantial attempt to put the claims into condition for allowance. In Paper No. 22 several claims were cancelled (claims 1-2, 4-6, 8 and 11-16) and several claims were amended (claims 3, 7, 17-18). Claims 3, 7, 9-10 and 17-18 are pending in the instant application.

Upon further review of the prior art and instant specification, it has been determined that claims 7, 17 and 18 are not allowable for reasons given below. Therefore, applicants are hereby notified that prosecution in this application is reopened. Any rejection of record that has not been addressed herein is withdrawn.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).
The residence of Urszula Wojda has been altered.

Drawings

Applicants are reminded that the originally filed drawing was found to be unacceptable by the draftsperson (see the PTO Form 948 mailed with Paper No. 9 mailed 11/7/00).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 17 is drawn towards a method of delivering a biologically active molecule to a cell comprising covalently linking biotin to the surface of the cell and contacting the covalently-linked biotin with an avidin/biologically active molecule complex such that the biologically active molecule is delivered to the cell surface. Although the specification indicates that the preferred cell type for use in the methods of the invention is a cell comprising a nucleus that is able to undergo endocytosis (e.g. page 6, lines 11-12), the term "cell" as used in the rejected claim could reasonably be interpreted to encompass cells lacking a nucleus (e.g. erythrocytes).

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ulevitch et al (U.S. Patent No. 6,045,795; see the entire patent).

Ulevitch et al teach a method for coating Sheep erythrocytes (E) with a lipopolysacharride-binding protein (LBP) wherein both E and LBP are biotinylated and where E and LBP are linked by streptavidin. In addition, the patent teaches that preliminary experiments were done where flourescein-labeled streptavidin was used to coat the biotinylated red blood cells (column 13, lines 28-49). In each case, biotin is covalently attached to the surface of the cell and a biologically active molecule (e.g. flourescein or LBP) is delivered to the cell as part of a streptavidin complex.

The '795 patent does not explicitly teach that avidin can be used in their methods.

The instant application admits that avidin and streptavidin can be used interchangeably in the methods of the instant invention (page 8, lines 18-19).

It would have been obvious to one of ordinary skill in the art to practice the methods taught by Ulevitch et al for determining the characteristics of LBP using avidin in place of streptavidin because, as the instant application admits, the two molecules are interchangeable as ligands in methods where biotin is used as an artificial receptor for delivery of a desired molecule to the surface of a cell. One would have been motivated to do so in order to realize the expected benefit of using a ligand with well-characterized binding characteristics for biotin. Absent any evidence to the contrary, there would have been a reasonable expectation of success in using avidin in the teachings of the '795 patent regarding characterization of a protein that interacts with red blood cells.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* embodiments, does not reasonably provide enablement for *in vivo* methods of delivering a biologically active nucleic acid that are intended for therapeutic benefit. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (In re Wands, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary. All of these factors have been considered in full, with the most relevant factors outlined below.

Complexity of the Invention/Breadth of the Claims: The rejected claims are directed to the delivery of a biologically active nucleic acid to, or into, a target cell. As written the claims encompass both in vitro, ex vivo and in vivo embodiments. The specification teaches that the claimed methods for delivery of a biologically active molecule of the invention are intended to be used for therapeutic, prophylactic and diagnostic purposes. The specification teaches that the methods of the invention can be used to deliver a marker to a cell, and exemplifies an

embodiment where marker (Green Fluorescence Protein) is encoded by a plasmid that is delivered to the cell by use of the claimed methods. However, the only other disclosed utility for delivery of nucleic acids to a cell in vivo is for therapeutic purposes. Thus, the instant claims read on methods of gene therapy. Gene therapy is an exceedingly complex field of endeavor, involving the recognition of a gene whose expression might be expected to alleviate some specific disease or condition, construction of a means of delivery, a vector for expression of the gene and optimization of means of delivery and expression such that the desired gene is expressed in an efficacious manner in those cells in which treatment is needed.

State of the Art/Predictability of the Art: An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al (Nature (1997) 389:239-242) and Palù et al (J. Biotechnol. (1999) 68: 1-13) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. See Verma et al, p. 239, 1st paragraph; Palù et al, p. 1, Abstract. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-viral methods for gene delivery, Verma et al indicates that most approaches suffer from poor efficiency and transient expression of the gene (p. 239, col. 3, 2nd paragraph). Likewise, Luo et al (Nature Biotechnology (2000) 18:33-37) indicates that non-viral synthetic delivery systems are very inefficient. See p. 33, Abstract and col. 1, 1st and 2nd paragraphs. While all three references indicate the promise of gene therapy, it is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made

before gene therapy becomes a useful technique. See Verma et al, p. 242, col. 2-3; Palù et al, pp. 10-11; Luo et al , p. 33, col. 1, 1st paragraph.

The area of the invention is unpredictable. As discussed above, the method of in vivo or ex vivo gene therapy is highly complex and unpredictable. The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect.

Guidance of the Specification/Working Examples: The present specification provides little or no guidance to support the claimed invention for gene therapy applications. The specification discloses no specific therapeutic molecules and diseases to which the claimed process can be applied. There is no direction provided as to how to overcome the obstacle to gene therapy recognized by leaders in the field, i.e. low efficiency of gene delivery and transient gene expression. There are no working examples directed towards gene therapy.

Quantity of Experimentation Required: The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed methods. In order to determine how to use the method to treat a condition, one of skill in the art would have to determine what effect exogenous transgene expression would have in any cell type, whether the effect could be exploited for treatment of a disease, how to deliver the given nucleic acid to the appropriate target cells with specificity and efficiency, and how to get sufficient expression to induce at least some therapeutic effect. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to practice the claimed methods in the full, broad scope currently claimed.

Conclusion

Claims 3, 9 and 10 are allowed. Claims 7, 17 and 18 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

Ggl
March 19, 2003